原著論文

Stability Testing of Drug Substances Approved by the Japanese Government in 2015

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2015年に承認された医療用原薬の安定性試験

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要 旨

2015年に日本で承認された新医療用原薬に対し、安定性試験の現状を調査した。我々は、2015年に安定性試験の記述がある47の新医療用原薬を特定した。長期保存試験としては、27原薬が25± 2 ℃/60± 5 %相対湿度（RH）または30± 2 ℃/65± 5 %RH の条件下で、8 原薬が 5 ± 3 ℃で、1 原薬が－18℃で、5 原薬が－20± 5 ℃で、1 原薬が－65℃で、2 原薬が－70℃で、2 原薬が黒塗りのため不明であり、1 原薬は半減期が短いため実施されなかった。光安定性試験では、22原薬が安定で、14原薬が光不安定であり、10原薬は記載がなく、1 原薬は実施されなかった。光安定性試験で不安定であった原薬は、すべて遮光保存とされた。これらのことから、2015年に承認された新医療用原薬は、ICH ガイドラインに従って、適切に設定されていることがわかった。

キーワード

安定性試験、新医療用原薬、長期保存試験、加速試験、光安定性試験、ICH-ガイドライン

Abstract

To investigate the current status of stability testing in Japan, we identified 47 new drug substances that had undergone stability testing in 2015. Among these, 27 were tested at 25±2℃/60±5% relative humidity (RH) or at 30±2℃/65±5% RH, 8 were tested at 5±3℃, 1 was tested at −18℃, 5 were tested at −20±5℃, 1 was tested at −65℃, 2 were tested at −70℃, 2 were unknown because they were long-term testing items were left blank, and 1 was not enforced due to its short half life. . Photostability testing revealed 22 new drug substances that were optically stable and 14 that were optically unstable, and whereas 10 new drug substances lacked a description and 1 was not tested. New drug substances that were unstable in photostability testing were stored in darkness. The present data show adequate performance of new drug substances that were approved according to the ICH guidelines in Japan in 2015.

Key words

accelerated testing, ICH guideline, long-term testing, new drug substance, photostability testing, stability testing

Introduction

Stability test results are an essential requirement for New Drug Applications. Accordingly, this requirement is discussed in the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),[1] and revisions of the guidelines for stability testing have been performed several times.

The guidelines for stability testing of new drug substances are listed in Table 1 and comprise the following:

ICH–Q1A (R2) states that the stability data package for new drug substances and drug products is sufficient for registration within the European Union, Japan, and the United States.[1]

ICH–Q1B states that the intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that light exposure does not cause unacceptable changes.[2]

ICH–Q1C is an annex to the ICH–Q1A (R2) and recommends stability items to be submitted with new dosage forms by the original applicant, after the original submission for a new drug substance or product.[3]

ICH–Q1D provides recommendations concerning the application of bracketing and matrixing in stability studies.[4]

ICH–Q1E provides recommendations on how to use stability data that is generated in accordance with the principles detailed in ICH –Q1A (R2), and those can be used to inform re-test periods and shelf lives in applications for registration.[5] Additionally, this guideline describes when and how extrapolation can be used to inform a re-test periods for drug substances, and to determine the shelf life of drug products that extend beyond the period covered by "available data from the stability studies under long-term storage condition."[5]

According to ICH–Q1A (R2), New Drug Applications require long term and acceleration studies to be included among stability tests.

Herein, we analyzed and discussed stability testing data for drug substances that were approved by the Japanese government in 2015.

MATERIALS AND METHODS

We surveyed drugs that were approved from January to December 2015. Information was retrieved from data summaries (Module 2 of Common Technical Document (CTD) in the present system) that were submitted bas New Drug Applications, and from approval documents that describe specifications and test methods for drug substances. This information, especially from the quality section, is not all publicly available, although

Table 1 Guidelines for stability testing of new drug substances

Name of Guideline	Abbreviation
Stability Testing of New Drug Substances and Products	ICH–Q1A (R2)
Stability Testing: Photostability Testing of New Drug Substances and Products,	ICH–Q1B
Stability Testing for New Dosage Form	ICH–Q1C
Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products	ICH–Q1D
Evaluation of Stability Data,	ICH–Q1E

Module 2 of the CTD and review reports are available on the internet.[6] Therefore, we do not disclose individual substance' names herein.

RESULTS AND DISCUSSION

Classification of Approved Drugs by Stability Testing

A total of 107 review reports were retrieved for 115 drug substances that were approved from January to December 2015, and those excluded antiseptics for medical devices, *in vivo* diagnostics, and generic drugs.

Initially, we classified drugs according to whether they had been subjected to stability test and among 115 drug substances 47 drugs had stability testing and 68 did not (Fig. 1).

The 68 bulk drug substances that had not been subjected to stability testing were drugs with new administration routes, new indications, or new dosages, and were not tested for stability according to the approval matter partial change application, which does not demand stability testing.

Whereas, 47 of 115 new drug substances (41%) had stability testing data, this rate of stability testing was 10% less than in 2014.[7]

Hence, further analyses were performed the 47 new drug substances with stability testing data.

Long-term Testing

According to ICH-Q1A (R2),[1] long-term testing for general new drug substances is performed at 25±2℃/60±5% relative humidity (RH) or 30±2℃/65±5%RH. However, for drug substances that are intended to be stored in a refrigerator, long-term testing is performed at 5±3℃, and for drug substances that are intended to be stored in a freezer, long-term testing is performed at −20±5℃. Additionally, long-term testing for drug substances that are intended for storage at −20℃ is performed on a case-by-case basis.

Long-term testing was performed at 25±2℃/60±5%RH or 30±2℃/65±5%RH for 27 new drug substances, at 5±3℃ for 8, at −18℃ for 1, at −20±5℃ for 5, at −65℃ for 1, at −70℃ for 2, and at unknown temperatures for

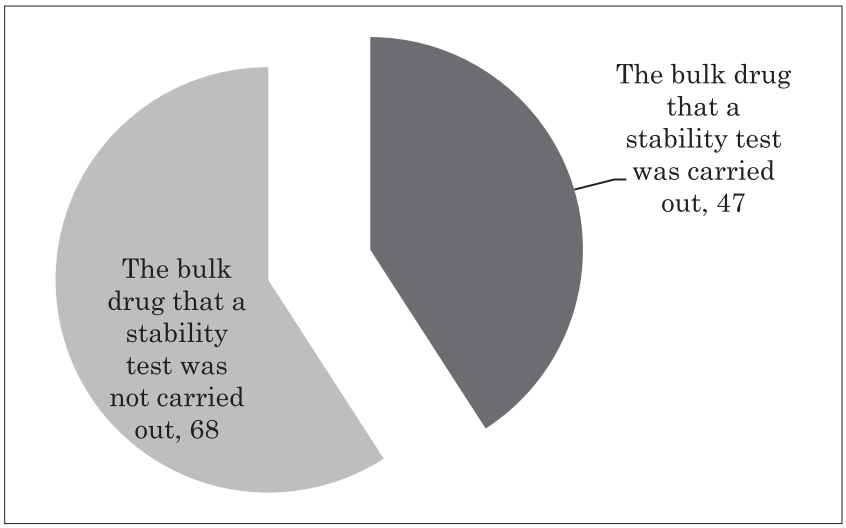

Fig. 1 Classification of New Drug Substances according to whether they were subjected to stability testing

2, for which the data was concealed (Table 2). One substance was not subjected to long term testing because its half life was too short.

Among the 47 new drug substances, 23, 6, 1, 2, 4 and 1 had shelf lives or re-test periods of > 36, 24, 21, 1, 12, 6 months, respectively, and 9 had unknown shelf lives or re-test periods (Table 2).

Moreover, 13 new drug substances that were scrutinized according to ICH-Q1E[5] had postponed expiration dates (Fig. 2).

Extrapolation to extend the retest period or shelf life beyond the period covered by long-term data can be proposed in the application, particularly if no significant change is observed under accelerated conditions. Specifically, the proposed retest period or shelf life can doubled at most, but should not be more increased than 12 months beyond the period covered by long-term data. As for Q1E application items, a long-term test of 12–24 months was performed, and we consider the shelf lives or re-test periods of these new drug substances adequate.

Similarly long-term testing data indicates that the shelf lives or re-test periods of new drug substances are set and evaluated adequately.

Table 2 Specific storage temperatures and conservation period in long-term testing

Storage Condition	Shelf Life or Re-Test Period (month)	Number of New Drug Products
30±2℃/65±5%RH	36	1
	18	1
	12	1
	Unknown*	1
25±2℃/60±5%RH	60	9
	48	5
	36	1
	24	4
	18	1
	12	2
	Unknown*	1
5±3℃	36	2
	24	2
	12	1
	6	1
	Unknown*	2
−18℃	48	1
−20±5℃	60	2
	Unknown*	3
−65℃	48	1
−70℃	36	1
	21	1
Unknown*	Unknown*	2
No enforcement**	No enforcement**	1

*: Blank entries are recorded as unknown.
**: Long-term testing was not performed because the half life was too short.

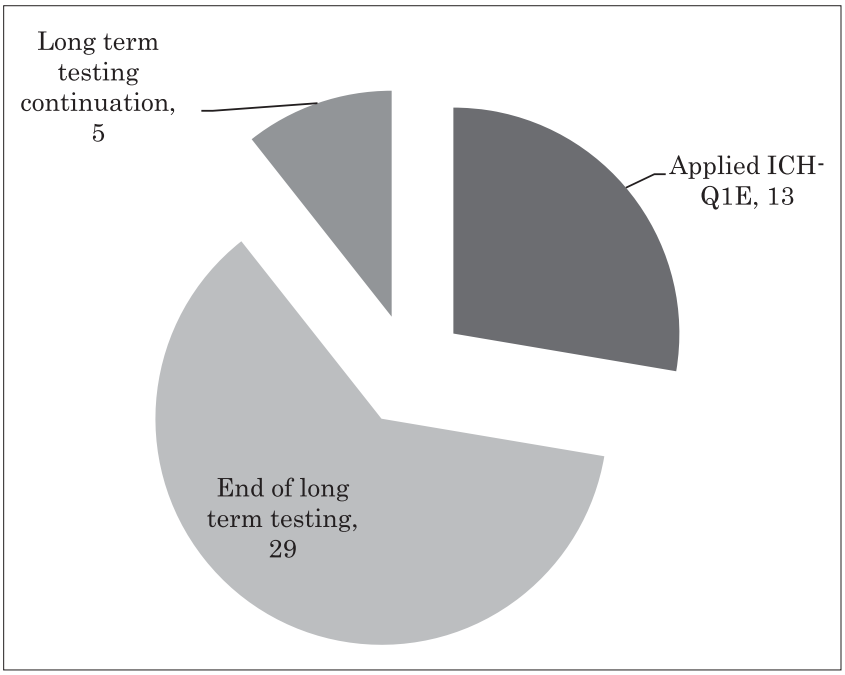

Fig. 2 Numbers of ICH–Q1E applications

Accelerated Testing

According to ICH–Q1A (R2),[1] accelerated testing for general new drug substances is performed at 40±2℃/75±5% RH. For drug substances that are intended for storage in a refrigerator, accelerated testing is performed at 25±2℃/60±5%RH.

We found that accelerated testing was performed at 40±2℃/75±5%RH for 27, at 25±2℃/60±5% RH for 7, at 6℃ for 1, at 5℃ for 2 new drug substances, and the temperatures for 3 substances were concealed and were not listed for 7 substances.

Accelerated testing was performing for 6 months at 40℃ for all but one substance, which was tested for 12 months. In addition, the duration of accelerated testing was concealed for one substance. All other substances were stable in accelerated tests.

Among accelerated tests that performed at 25℃, one was performed for 12 months and the others performed for 6 months. One of substance, a genetic recombination, did not satisfy the specification of 6 months.

New drug substances that were subjected to acceleration testing at 6℃ for 6 months reportedly had remarkable resolution. In contrast, new drug substances that were subjected to accelerated testing at 5℃ for 6 months were stable.

Three new drug substances that were tested at unknown temperatures included a genetic recombination and 2 vaccines. Because accelerated testing information is subjected to intellectual property laws, we were unable to show them.

Seven new drug substances with no reported accelerated testing included a genetic recombination, extracts, a radioactive isotope, a vaccine, and drug master file registration products. According to ICH–Q1A (R2),[1] new drug substances that are stored in a

freezer do not require accelerated testing. Hence, these new drug substances do not have accelerated testing data.

Collectively, the results of accelerated testing indicate, that shelf lives or re-test periods of new drug substances are set and evaluated adequately.

Photostability Testing

According to ICH–Q1B,[2] photostability testing of drug substances comprises forced degradation testing and confirmatory testing. The purpose of forced degradation testing is to evaluate overall photostability of the material for methods development purposes, and/or to elucidate degradation pathways. Hence, a variety of exposure conditions are used in forced degradation studies, sometimes producing decomposition products that are unlikely to be formed under the conditions used for confirmatory studies. This information facilitates the development and validation of analytical methods, and confirmatory studies are conducted to inform packaging and labeling.

Twenty-two new drug substances were optically stable and 14 were unstable. Although 10substances did not have photostability data, we assume that photostability testing was performed (Fig. 3). Because most new drug substances are preserved under shaded condition, we conclude that the storage conditions are appropriate.

In conclusion, the present review included 47 new drug substances that were approved in Japan in 2015 according to ICH guidelines, and all performed adequately.

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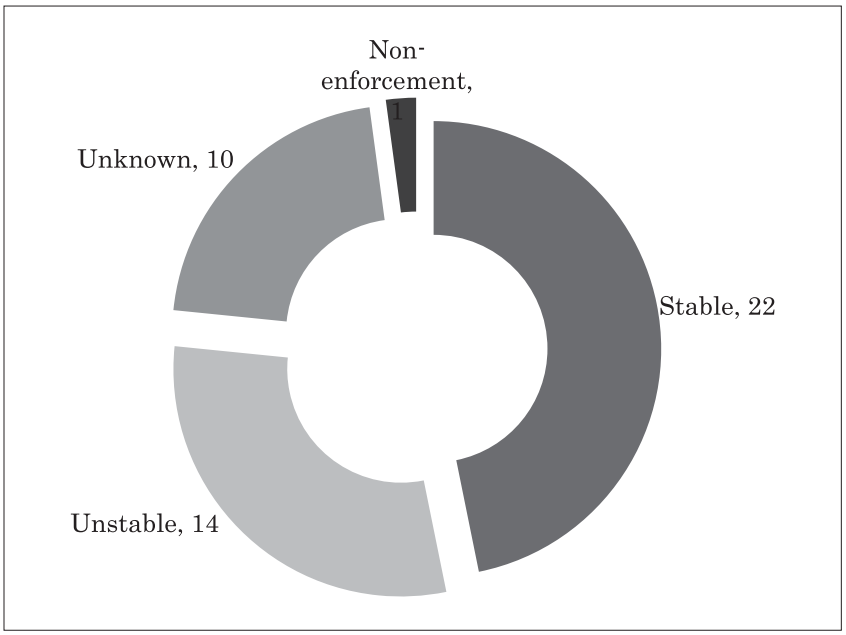

Fig. 3 Itemization of photostability testing

statements. No official support or endorsement by the Pharmaceuticals and Medical Devices Agency is intended, nor should be inferred.

Conflict of Interest

The authors declare no conflict of interest.

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